This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Benfuracarb

(Pesticides)

Food Safety Commission of Japan (FSCJ)
February 2020

ABSTRACT

FSCJ conducted the risk assessment of a carbamate insecticide, benfuracarb (CAS No. 82560-54-1), based on various documents.

The data used in the assessment include fate in animals (rats and goats), fate in plants (paddy rice and kidney beans), residue in crops, acute neurotoxicity (rats), subacute toxicity (rats and mice), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproduction toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity. Studies on ChE inhibition in rats and dogs were also assessed.

Major adverse effects of benfuracarb observed are inhibition of brain and RBC ChE activity, and suppressed body weight. Benfuracarb showed no carcinogenicity, teratogenicity and genotoxicity.

In a two-generation reproduction toxicity study in rats, reduced number of newborn offspring was observed.

The relevant substance for the residue definition for dietary risk assessment in agricultural products and that in fishery products were identified as benfuracarb, its metabolite B (carboflan) and C (including conjugated form of both), and benfuracarb and its metabolite B (carboflan) respectively.

The lowest value of the NOAEL or LOAEL in all tests was the 0.89 mg/kg bw/day of NOAEL in a 90-day subacute toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.0089 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

As for potential adverse effects of a single oral administration of benfuracarb, FSCJ used ChE activity inhibition as the toxicity index of the highest sensitivity. Comprehensively considering the detection timing and the detected results of ChE activity in each study, FSCJ recognized that the LOAEL of 1.84 mg/kg bw/day, obtained in a 90-day subacute neurotoxicity study, as the lowest value in all tests. Accordingly, FSCJ specified an acute reference dose (ARfD) to be 0.0092 mg/kg bw by applying a safety factor of 200 (10 for interspecies difference, 10 for Interindividual difference, and additional factor of 2 for using LOAEL) to the LOAEL.
The lowest value of LOAEL for metabolite B (carbofuran), 0.03 mg/kg bw obtained in the comprehensive evaluation on ChE activity inhibition in rats, was lower than that of benfuracarb. FSCJ specified an ADI

and an ARfD for the metabolite B (carbofuran) as 0.00015 mg/kg bw/day and 0.00015 mg/kg bw respectively, applying a safety factor of 200 (10 for interspecies difference, 10 for Interindividual difference, an additional factor of 2 for using LOAEL) to the LOAEL.

Table 1. *Levels relevant to toxicological evaluation of benfuracarb*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints [1)]
Rat	90-day subacute toxicity study (the 1st study)	0, 200, 400, 800 ppm M: 0, 13.6, 27.9, 58.0 F: 0, 15.7, 32.5, 67.7	M/F: - M/F: Decreased Glu
	90-day subacute toxicity study (the 2nd study)	0, 30, 300, 900/1 000/1 200 ppm M: 0, 2.14, 26.2, 85.4 F: 0, 2.55, 31.9, 103	M: 2.14 F: - M: Suppressed body weight F: RBC ChE activity inhibition (more than 20 %)
	90-day subacute neurotoxicity study	0, 30, 120, 480 ppm M: 0, 1.84, 7.64, 31.5 F: 0, 2.09, 8.60, 36.7	M: - F: 2.09 M: RBC ChE activity inhibition (more than 20 %) F: RBC and brain ChE activity inhibition (more than 20 %)
	One-year chronic toxicity study	0, 200, 400, 800 ppm M: 0, 11.9, 24.7, 51.3 F: 0, 14.0, 28.7, 62.9	M/F: - M/F: Suppressed body weight
	Two-year carcinogenicity study (the 1st study)	0, 100, 200, 400 ppm M: 0, 5.5, 11.3, 23.3 F: 0, 6.7, 13.7, 29.0	M: - F: 6.7 M/F: Suppressed body weight (No carcinogenicity)
	Two-year carcinogenicity study (the 2nd study)	0, 25 ppm M: 0, 1.5 F: 0, 1.8	M: 1.5 F: 1.8 M/F: No toxicity (No carcinogenicity)
	Comprehensive evaluation of two-year carcinogenicity study (the 1st and 2nd study)		M: 1.5 F: 6.7
	Two-generation reproduction study	0, 30, 100, 300 ppm	Parent and offspring PM: 1.89 PF: 2.29 F_1M: 2.28 F_1F: 2.59 Reproductive activity

		PM: 0, 1.89, 6.46, 18.8 PF: 0, 2.29, 7.78, 23.1 F_1M: 0, 2.28, 7.62, 24.2 F_1F: 0, 2.59, 8.94, 28.3	PM: 6.46 PF: 7.78 F_1M: 7.62 F_1F: 8.94 Parent: Suppressed body weight Offspring: Suppressed body weight Reproductive activity: Reduced survival rate
	Developmental toxicity study	0, 2, 10, 40	Dams: 2 Fetuses: 10 Dams: Suppressed body weight Fetuses: Low body weight (No teratogenicity)
Mouse	90-day subacute toxicity study	0, 100, 300, 1 000 ppm M: 0, 16.3, 47.1, 162 F: 0, 22.8, 62.7, 222	M: 47.1 F: 62.7 M/F: Decreased body weight/suppressed body weight
	18-month carcinogenicity study	0, 100, 300, 1 000 ppm M: 0, 15.4, 45.1, 152 F: 0, 19.3, 56.5, 190	M: 45.1 F: 19.3 M/F: Suppressed body weight (No carcinogenicity)
Rabbit	Developmental toxicity study	0, 5, 10, 15	Dams: 5 Fetuses: 10 Dams: Death Fetuses: Low body weight (No teratogenicity)
Dog	90-day subacute toxicity study	0, 25, 100, 400/500 ppm M: 0, 0.95, 4.33, 13.8 F: 0, 0.89, 4.14, 14.3	M: 0.95 F: 0.89 M/F: Thymic involution
	6-month subacute toxicity study	0, 2.5, 5, 10	M/F: 2.5 M: RBC ChE activity inhibition (more than 20 %) F: Spasm, hind limb ataxia

	Two-year chronic toxicity study	0, 2.5, 5.0, 10.0	M/F: 2.5 M/F: Mucous stool, spasm, hind limb ataxia
	Comprehensive evaluation of 90-day and 6-month subacute toxicity study and two-year chronic toxicity study		
ADI			NOAEL: 0.89 SF: 100 ADI: 0.0089
The critical study for setting ADI			90-day subacute toxicity study

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor
-, NOAEL could not be specified
/, No description in relevant references
[1)], The adverse effect observed at LOAEL

Table 2. *Potential adverse effects of a single oral administration of benfuracarb*

Species	Study	Dose (mg/kg bw/day or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1)]
Rat	Acute toxicity study	67 (Female only), 80, 96, 116, 139, 167	M/F: - M/F: Whole body trembling, salivation, lacrimation
	Acute toxicity study	0, 135, 165, 202, 246, 300	M/F: - M/F: Fasciculation, salivation, tremor
	Acute neurotoxicity study	0, 1.6, 8, 40	M/F: 1.6 M/F: Spasm, miosis [a)]
	ChE activity inhibition test	M: 0, 110, 143	- RBC and brain ChE activity inhibition (more than 20%)
	90-day subacute toxicity study (the 1st study)	0, 200, 400, 800 ppm M: 13.6, 27.9, 58.0 F: 15.7, 32.5, 67.7	M: 58.0 F: 67.7 No effects on RBC and brain ChE activity
	90-day subacute toxicity study (the 2nd study)	0, 30, 300, 900/1 000/1 200 ppm M: 2.14, 26.2, 85.4 F: 2.55, 31.9, 103	M: 2.14 F: - M: Tremor F: RBC ChE activity inhibition (more than 20%)
	90-day subacute neurotoxicity study	0, 30, 120, 480 ppm M: 1.84, 7.64, 31.5 F: 2.09, 8.60, 36.7	M: - F: 2.09 RBC ChE activity inhibition (more than 20%)
	One-year chronic toxicity study	0, 200, 400, 800 ppm M: 11.9, 24.7, 51.3 F: 14.0, 28.7, 62.9	M: 51.3 F: 62.9 No effects on RBC and brain ChE activity
	Two-year carcinogenicity study (the 1st study)	0, 100, 200, 400 ppm M: 5.5, 11.3, 23.3 F: 6.7, 13.7, 29.0	M: 5.5 F: 13.7 M: RBC ChE activity inhibition (more than 20%)

	Two-year carcinogenicity study (the 2nd study)	M: 0, 25 ppm M: 1.5 F: 1.8	M: 1.5 F: 1.8 No effects on RBC and brain ChE activity
Mouse	Acute toxicity study	64, 80, 100, 125, 156	M/F: - M/F: Whole body trembling, salivation
	90-day subacute toxicity study	0, 100, 300, 1 000 ppm M: 16.3, 47.1, 162 F: 22.8, 62.7, 222	M: 47.1 F: 62.7 Calmness, piloerection, ptosis
Dog	Acute toxicity study	M: 175, 300, 520 F: 175, 230, 300	M/F: - M/F: Soft stool/watery stool, ataxic gait, spasm
	6-month subacute toxicity study	0, 2.5, 5.0, 10.0	M/F: 2.5 M/F: mucous stool, spasm, hind limb ataxia
	Two-year chronic toxicity study	0, 2.5, 5, 10	M/F: 2.5 M/F: mucous stool, spasm, hind limb ataxia
ARfD			LOAEL: 1.84 SF: 200 ARfD: 0.0092
The critical study for setting ARfD			90-day subacute neurotoxicity study in rats

ARfD, Acute reference dose; LOAEL, Lowest-observed-adverse-effect level; SF, Safety factor;
-, NOAEL could not be observed.
[1)], The adverse effect observed at LOAEL
[a)], RBC and brain ChE activity inhibition was not used in assessment, considering the timing of the test.